PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ON/4-33648A	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2005/001180	International filing date *(day/month/year)* 04.02.2005	Priority date *(day/month/year)* 05.02.2004
International Patent Classification (IPC) or national classification and IPC INV. A61K45/06		
Applicant NOVARTIS AG et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21.11.2005	16.01.2007
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Olausson, Jenny Telephone No. +31 70 340-

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2005/001180

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-11 as originally filed

   Claims, Numbers

   1-12 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 3, 5-9, 11 partly

because:

☒ the said international application, or the said claims Nos. 3, 5-9, 11 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

☐ no international search report has been established for the said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5
	No:	Claims	1-4, 6-12
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-12
Industrial applicability (IA)	Yes:	Claims	1, 2, 4, 10, 12
	No:	Claims	3, 5-9, 11

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item I

Basis of the report

The examination is being carried out on the following application documents:

Description, Pages
1-11 as originally filed

Claims, Numbers
1-12 as originally filed

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 3, 5-9 and 11 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

For the assessment of the present claims 3, 5-9 and 11 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Reference is made to the following documents:

D1: ARNT C R ET AL: "SYNTHETIC SMAC/DIABLO PEPTIDES ENHANCE THE

EFFECTS OF CHEMOTHERAPEUTIC AGENTS BY BINDING XIAP AND CIAP1 IN SITU" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOCHEMICAL BIOLOGISTS, BIRMINGHAM,, US, vol. 277, no. 46, 15 November 2002 (2002-11-15), pages 44236-44243, XP001155278 ISSN: 0021-9258

D2: WO 03/045974 A (THE BURNHAM INSTITUTE; TORREY PINES INSTITUTE FOR MOLECULAR STUDIES; R) 5 June 2003 (2003-06-05)

D3: FANG GUOFU ET AL: "CGP57148B (STI-571) induces differentiation and apoptosis and sensitizes Bcr-Abl-positive human leukemia cells to apoptosis due to antileukemic drugs" BLOOD, W.B.SAUNDERS COMPANY, ORLANDO, FL, US, vol. 96, no. 6, 15 September 2000 (2000-09-15), pages 2246-2253, XP002217133 ISSN: 0006-4971

D4: HU Y ET AL: "ANTISENSE OLIGONUCLEOTIDES TARGETING XIAP INDUCE APOPTOSIS AND ENHANCE THERAPEUTIC ACTIVITY AGAINST HUMAN LUNG CANCER CELLS WHEN COMBINED WITH ANTICANCER DRUG IN VITRO AND IN VIVO" PROCEEDINGS OF THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, NEW YORK, NY, US, vol. 43, March 2002 (2002-03), page 576, XP008023559 ISSN: 0197-016X

D5: US 2003/190659 A1 (LACASSE ERIC ET AL) 9 October 2003 (2003-10-09)

D6: WO 2004/005248 A (NOVARTIS AG; NOVARTIS PHARMA GMBH; SHARMA, SUSHIL, KUMAR; ZAWEL, LEIGH) 15 January 2004 (2004-01-15) cited in the application

Novelty (Article 33(2) PCT):

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-4 and 6-12 is not new in the sense of Article 33(2) PCT.

Document D1 discloses peptides inhibiting IAP (abstract, figure 1). Combining those peptides with doxorubicin, (a topoisomerase II inhibitor) etoposide (a topoisomerase II inhibitor), or SN-38 (a topoisomerase I inhibitor) enhances the chemotherapy-induced apoptosis in human breast cancer cell lines (abstract and page 44238, column 2). The subject-matter of claims 1-4 and 6-12 is therefore not new (Article 33(2) PCT).

Furthermore, the documents D2-D5 anticipate the subject-matter of claims 1-4, 7, 8, 11 and 12:
Document D2 discloses small molecule antagonists of XIAP (figure 12) that show a synergistic effect together with etoposide (a topoisomerase II inhibitor) in inducing apoptosis in cancer cell lines (figure 13).
Document D3 discloses compound CGP57148B which lowers XIAP levels (page 2249, column 2). Combination of this compound with etoposide and doxorubicin (topoisomerase II inhibitors) increases apoptosis in leukemia cell lines (page 2252).
Document D4 discloses that antisense nucleotides targeting XIAP enhance therapeutic activity of anticancer drugs such as doxorubicin and etoposide (topoisomerase II inhibitors) in human lung cancer cell lines (the whole document).
Document D5 discloses oligonucleotides inhibiting IAP (paragraph 11) for the treatment of cancer (paragraph 16). Furthermore it discloses combining those nucleotides with anticancer drugs such as doxorubicin, taxol, vinorelbine, etoposide (paragraph 157).

Inventive step (Article 33(3) PCT):
The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-12 does not involve an inventive step in the sense of Article 33(3) PCT.

The document D6 is regarded as being the closest prior art and discloses (the references in parentheses applying to this document):

The presently claimed compounds C and D as being IAP inhibitors (examples 1 and 15) and their use for the treatment of proliferative diseases such as cancer (page 1, paragraph 1). Document D6 also indicates that a combination of the presently claimed compounds C and D with other anticancer agents is advantageous (page 11, paragraph 5). Among the anticancer agents useful for a combination therapy are anti-tumor antibiotics and alkylating agents (page 12, paragraph 1).

The difference between document D6 and the present claims is the use of an unspecified anticancer agent instead of a topoisomerase I or II inhibitor as presently claimed. The problem to be solved by the present invention may therefore be regarded as how to provide alternative compositions comprising an IAP inhibitor and a anticancer agent.

The solution proposed in the present claims cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

From document D6, combinations of IAP inhibitors, including the presently claimed compounds C and D, and many classes of antineoplastic compounds (including e.g. anti-tumor antibiotics and alkylating agents) are known. Topoisomerase inhibitors are another class of obvious alternative anti-tumor antibiotics respectively alkylating agents. It is clear that a skilled person would, without inventive effort, also combine IAP inhibitors with topoisomerase inhibitors. This has indeed been done in document D1 for as well topoisomerase I and topoisomerase II inhibitors with comparable beneficial effect. In the absence of any indication to an unexpected technical effect in the present application, claims to the combination lack an inventive step (Article 33(3) PCT).

In view of the available prior art, it would seem that the selection of compound C and D (see present claim 5) together with any topoisomerase is obvious; however, the prior art focuses on combinations with topoisomerase II inhibitors. Furthermore, if data comparable to the tables on page 11 can be provided for example 2 (topotecan and compound C), it would seem credible that compounds C and D will give rise to synergism with any topoisomerase I inhibitor.